FOSTERING COMMUNICATION AND COLLABORATION

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AN EXIT INTERVIEW: PARTING THOUGHTS FROM NCI'S BRODER

by Rebecca Kolberg

After more than two decades with NCI, during which he rose from a clinical associate in the Metabolism Branch to institute director, Samuel Broder is venturing into the private sector. Before Broder packed his bags in April to join Ivax Corp., a growing drug research and development firm based in Miami, he gave *The NIH Catalyst* a few minutes for a free-wheeling discussion that touched on everything from NIH's institute structure to his concept of "term limits" for high-ranking NIH administrators.

Samuel Broder

Q: How has the NIH intramural research program changed since you started here in 1972?

Broder: I think the scientific opportunities are much greater now. Scientists and clinicians are able to ask a lot more interesting questions and, in effect, get a lot more done in a limited amount of time. Some of the changes in how careers in government are viewed in the current political climate don't make me that happy. I think government service is substantially less valued now than when I first came here.

Q: What advice do you have for young scientists just starting out at NIH today?

Broder: To recognize the unbelievable opportunities that exist in the

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OFFICE OF TECHNOLOGY TRANSFER: FROM CHASING ITS TAIL TO BLAZING A TRAIL

by Celia Hooper

Maria Freire

Considering that she has just taken her place in one of the hottest of NIH's hot seats, Maria Freire is remarkably calm, collected, and personable. The new head of NIH's perennially beleaguered Office of Technology Transfer (OTT) assumed the position in February and since then, has been systematically taking inventory, setting priorities, and making contacts with NIH's technology development coordinators and the scientific directors who supervise the research that OTT patents, licenses, and markets. Her arrival comes just as NIH is becoming a highly visible player on the biomedical tech-transfer scene, with its decision to drop controversial patent claims to hundreds of cDNAs isolated by former NIH researcher Craig Venter, its successful negotiations over the *BRCA1* gene patent, and its success in winning a very broad patent on ex vivo gene therapy licensed to Genetic Therapy Inc., the Gaithersburg, Md., firm that was NIH's partner in a Cooperative Research and Development Agreement (CRADA) for the method.

"We have a legal mandate to transfer technology at NIH, so it's not a question of should we do it but, rather, how do we do it appropriately — how can we lower the barriers to technology transfer for scientists and get the technology to the bedside?" Freire asks.

A chorus of inventors at NIH would have some swift and grumpy answers for her. And basic scientists who are unlikely ever to use OTT's services have their own qualms about the effects that tech transfer may have on the research community.

Says one intramural inventor, "Tech transfer at NIH is in miserable shape." Her complaints include frustrations getting through to the correct person via OTT's mazelike voice-mail system — or getting a call, fax, or letter answered promptly after she does get through. "I have had a major licensing problem. A license expired three years ago and still has not been renegotiated, even though four companies have

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NATIONAL INSTITUTES OF HEALTH: THE SHAPE OF THINGS TO COME, PART I

Michael Gottesman

Futurism is back in style. At the risk of being overtaken by events beyond our control, it's often tempting to follow the lead of H.G. Wells and conjure up a picture of what the future may hold. At times of change — such as the present — it is reassuring to hear that our most cherished institution, that is, NIH, will be thriving in years to come. This two-part commentary is intended to give NIH scientists and support staff a glimpse into the likely future of our institution. Part I will address how the evolution of NIH's physical environment will shape our scientific lifestyle. Part II will detail science-management issues that affect the way we conduct research. The opinions expressed in this commentary are strictly my own and are based on what I see as the most likely course of events for NIH over the next couple of decades. Here are the assumptions:

- NIH's overall budget will remain stable, barely keeping pace with inflation. The intramural share of this budget will be subject to even greater pressure to decrease it, reflecting the current move to "downsize" all government activities and the requirement that we reduce intramural full-time employees by an additional 5% over the next four years. Current projections of a 3% growth in the intramural budget translate into a 1% to 2% drop in buying power each year based on the current rate of biomedical inflation.
- The current population of the Bethesda campus — approximately 16,350 people — will grow very little, if at all, over the next 20 years. The highest estimates of NIH's population, which are based on potentially moving some outlying scientific programs back to the main campus, project no more than 10% growth over the next two decades. To me, a no-growth scenario seems most likely, with a continuing decline in the existing NIH campus population being barely offset by the transfer of outlying programs back to the main campus.
- NIH will be responsive to lifestyle concerns raised by our staff and neighbors so that we can work in safe laboratories on an aesthetically pleasing campus. We will continue to reduce the creation of hazardous waste, to improve disposal of hazardous waste, and to recycle nonhazardous solid waste. We also want to serve as a model and a resource for the community in matters of science and cultural activities, health-related concerns, and noise and traffic abatement.

The 1972 NIH Campus Master Plan — the major document guiding physical changes on the main campus — is now obsolete. A new Master Plan spanning the next 20 years is currently being drafted by the Office of Research Services. That plan, which must be submitted to Congress and the National Capital Park and Planning Commission by June 30, allows NIH to change its buildings and its infrastructure, such as electrical lines and roads, without getting explicit approval for each change, but still requires individual environmental studies. As might be expected, there is enormous interest in the new plan. The Office of Research Services is planning a number of opportunities for broad NIH input, and every scientific director on campus has already been interviewed. Meanwhile, Janyce Hedetniemi, director of the Office of Community Liaison, has established a working group of 35 community leaders to provide community input into the final product.

The new Master Plan will likely contain many of the following features: 1) modification of roads, walks, and bike paths to make the campus easily accessible to all, 2) demolition of Buildings 7 and 9 — obsolete structures unsuitable for 21st century science, 3) conversion of historically significant Buildings 2 and 3 into office space, 4) construction of two new buildings — a consolidated laboratory to replace Buildings 2, 3, and 7 and a new hospital with associated labs that will likely be attached to the north side of the existing Clinical Center, and 5) renovation of older research buildings, especially labs in the Clinical Center.

The overall effect of these changes will be to improve the utility, safety and appearance of NIH. Given the declining number of scientists on campus and a small net increase in total lab space, the average space per researcher should increase. From my perspective, this is an extremely positive development. Currently, our labs are entirely too crowded and our hallways are groaning with equipment and supplies. Relief is needed. In the short term, we must exercise restraint in the number of people we cram into available space. In the long term, the combination of a bit more space and enforced downsizing should improve our lab conditions.

Improvement is also on the horizon when it comes to the environmental challenges that face NIH and our neighbors. The Environmental Concerns Working Group, which has NIH and community membership, has set up several subcommittees to address concerns about medical pathological waste (MPW), bulk mail, and community health. The subcommittees have already made the following recommendations:

- Continue to reduce the generation of MPW. Although MPW has been cut 19% in the past few months, an additional 20% to 30% reduction should be attainable through more judicious use of MPW boxes. Analyze options for "closed" sterilization systems to replace the need to truck MPW to Baltimore for incineration.
- Extend white-paper and aluminum-can recycling to more parts of campus. Begin interim plans to recycle polypropylene pipet-tip holders and other plastics. Prepare for a long-range plan to recycle 50% of the solid waste on campus — an effort that has been initiated, but will take about two years to fully implement.
- Solicit short-term solutions for reducing unwanted bulk mailings. Lay the groundwork for replacing paper catalogs with electronic ordering systems over the next few years.
- Analyze epidemiological data for Bethesda to determine whether any environmentally related disorders occur more frequently near NIH than elsewhere.

As an NIH scientist, before taking the helm of the Office of Intramural Research, I often felt that things just happened on campus without any input from scientists. Therefore, I want to seek your advice and keep you informed about the shape of things to come. Send your comments on this article to me via computer (e-mail: gottesmm@od1em1.od.nih.gov) or FAX-BACK to *The NIH Catalyst* (fax: 402-4303).

Michael Gottesman
Deputy Director for Intramural Research

Time marches on. *NIH's Bethesda campus circa 1951. Note that the Clinical Center is just under construction.*

Calendar Subscription

Although you may miss the familiar color for a while, NIH's weekly "Yellow Sheet," or Calendar of Events, is available by electronic subscription. To receive the calendar via e-mail, send an e-mail message to listserv@list.nih.gov with the message: "SUBSCRIBE CALENDAR Your Name" ■

Neuroendocrinology Symposium

As a satellite to the Endocrine Society Conference in Washington, D.C., a symposium entitled "Four Decades of Neuroendocrinology: A Tribute to S.M. McCann" will be held June 13 from 2 to 6 p.m. at Masur Auditorium in Building 10. The symposium will span the many areas of neuroendocrinological research, including gonadotropins, atrial natriuretic peptide, and hormones of the hypothalamic-pituitary-adrenal axis.

Samuel McDonald McCann, who earned his M.D. from the University of Pennsylvania School of Medicine in Philadelphia in 1948, has made seminal contributions to the understanding of neuroendocrine regulation of growth, reproduction, thyroid function, and responses to stressful stimuli. Most recently, McCann's research has centered on neuroendocrine immunology and interactions between the immune system and the central nervous system.

McCann, who is a professor of biomedical science at the University of Texas, Southwestern Medical Center at Dallas, is a member of the National Academy of Sciences and a past president of the International Society of Neuroendocrinology. ■

DDIR's Bulletin Board Made Easy

If you're one of those people who prefer getting a newspaper delivered to your doorstep rather than standing in line at a newsstand or wrestling with a vending box, you'll welcome the latest advance in the delivery of the Deputy Director for Intramural Research's Bulletin Board: electronic subscription. With this new, time-saving service, intramural scientists can get the latest information emanating from Building 1 delivered directly to their e-mail boxes, instead of digging it out of Gopher's or the World Wide Web's "NIH Campus Info" menu. Sign up soon, because some updates, such as late seminar announcements, may be posted only to e-mail subscribers. To subscribe, send an e-mail message that reads "Subscribe DDIRBB-L Your Name" to this BITnet address: listserv@list.nih.gov ■

Research Festival Deadline

The deadline for the 1995 NIH Research Festival is quickly approaching. Researchers from all institutes, centers, and divisions have until 5 p.m. June 2 to submit 120-word abstracts for posters or workshops at the festival, which will be held Sept. 18-22 in the Natcher Building. In a change from past years, it will be up to the festival organizing committee to assign scientists' proposed presentations to the festival's four poster sessions or to one of the event's 24 workshops. If you have not received an application form via campus mail or would like more information, contact Gregory Roa at the NIH Visitor Information Center (phone: 496-1776). ■

FAX-BACK Feedback

Below are FAX-BACK comments we received for topics raised in the November-December and January-February issues.

On investigating scientific-misconduct allegations

I do not think that NIH should waste time and effort in attempting to set up internal mechanisms for the examination of alleged misconduct. [see Science Ethics Forum, November-December 1994 issue] My reason for this view is that institutions are inherently incapable of investigating themselves honestly. The historical record shows that intra-institutional pressures, extraneous to the scientific-misconduct issue, have invariably produced whitewash and/or cover-up. For example, a faculty member charged with investigating alleged misconduct at his own institution may be conflicted between fact finding and the pressure to be a "team player." Therefore, he or she might not find misconduct that could possibly result in the loss of prestige and (more importantly) funds to the parent institution.

The Mikulas Popovic - Robert Gallo and the Thereza Imanishi-Kari - David Baltimore cases are the two most well-known but are not atypical examples of how the current system has "worked" in government and academic environments. The fact that these cases are still ongoing after approximately 10 years is a gross injustice to the accused, to the whistle-blowers, to all scientists, and to the public at large. Clearly, we need a new system.

The establishment of an organization that is devoted entirely to the fact-finding process and is wholly independent of government and of any particular university has been suggested. Universities and government agencies would agree in advance to accept the results of the objective investigations of this body. The existence of such an organization would eliminate intra-institutional conflict of interest and would also separate fact-finding from disciplinary actions, the latter being left to the relevant institutions. This organization should be directed by an outstanding individual of unimpeachable integrity and staffed primarily by people with scientific backgrounds and capable of critical analysis.

I call upon Dr. [Harold] Varmus to take a leadership role and convene a meeting for refining the many details involved in establishing such an organization. Such details would include, among others, procedural safeguards, mechanisms for obtaining documents, policies relating to confidentiality, and means of funding support for such an enterprise. Once it is accepted that some amount of scientific misconduct exists and that the current procedures have not worked satisfactorily, it should be possible to develop techniques to solve this problem.

— Philip D. Ross, NIDDK

On NIH's new affirmative action plan

The new affirmative action plan appears to be going in the right direction.[see Insights from OEO's New Leader, January-February 1995 issue]. The concepts — a) making the leadership at the top responsible but allowing them to be flexible to handle the problems inherent in small group statistics, b) comparing NIH representation to that in truly comparable nationwide groups, and c) focusing on education to reduce the real bottleneck in the process of creating minority professionals — all make sense. Most important is a spirit of cooperation to improve race relations and to increase the interest and ability of minorities in science, as opposed to an adversarial attitude.

We do note an egregious systematic error in the table on page 17. Only the URI [underrepresentation index] results for Hispanics and Native Americans are correct. If the computation is done as the asterik-marked footnote within the table dictates, grossly different results would be obtained. It appears that any result over 100% has been limited to 100% without mention. ... If one tries to excuse this on the grounds that "we forgot to mention that we limited the results because a URI over 100% is meaningless," with which we disagree since it is very informative of reverse discrimination, then how do you explain that the figure for men, which computes to about 69% on one table and 68% on the other, is also given as 100% ? One senior researcher in our lab has noted that if he submitted such data to a journal, he might never be allowed to publish again. ...

We wonder if you would be willing to publish a similar article, but corrected as above, in *The NIH Record*, with its very different readership, or do you have two standards?

— Anonymous

The Underrepresentation Index figure was based on tables provided by the Office of Employment Opportunity from its draft of the new NIH Affirmative Action plan. Because the plan's emphasis is on recruiting members of underrepresented groups, not removing members of overrepresented groups, placing an upper limit of 100% on the underrepresentation index (URI) seems appropriate. That aside, you are indeed correct that there is an error in the URI calculations for men. During the editing process, 100% was mistakenly inserted under the "men" category. As you note, the correct URI for men should be about 69% for the National Research Council data comparison and 68% for the 1990 Census data comparison. We apologize for the error.

As for publishing a similar article in The NIH Record, *you may be interested to know that* The NIH Catalyst, *published by the Office of Intramural Research by and for NIH scientists, is editorially independent from* The NIH Record, *which is published by the Office of Communications for the entire NIH community.* ■

The Electronic Catalyst

The NIH Catalyst is now available electronically. Current and back issues of the publication can be found in the Intramural Research News section under NIH Campus Information on Gopher or the World Wide Web. ■

THE FINAL CHAPTER ON THE FIAU STUDIES?

by Rebecca Kolberg

Almost two years after the FIAU ordeal began, NIH researchers are hoping the final chapter has at last been written with the release of an independent scientific report exonerating the clinical investigators who conducted the ill-fated trial.

The Institute of Medicine (IOM) report, issued in mid-March, is the third — and final — review of the circumstances surrounding the toxicity deaths of five patients receiving the experimental anti-hepatitis drug fialuridine (FIAU) in NIH clinical trials. The review was requested by HHS Secretary Donna Shalala, who wanted an outside scientific opinion in addition to reports from the Food and Drug Administration (FDA) and the NIH Director's Advisory Committee.

"It is my belief that the Institute of Medicine report should bring to a close this series of internal and external investigations of our fialuridine studies. The IOM articulated full support for clinical trials in chronic hepatitis B virus infection and of our actions in the three fialuridine studies conducted intramurally," says Stephen Straus, chief of the Laboratory of Clinical Investigation at NIAID, who led the FIAU studies along with Jay Hoofnagle, director of NIDDK's Division of Digestive Diseases and Nutrition.

Although Hoofnagle declines to comment on the specifics of the IOM report, he says, "It was obviously carefully and thoroughly done and provides very sound recommendations."

Like the NIH report issued in April 1994, the IOM panel, chaired by Morton Swartz, a professor of medicine at Harvard Medical School in Boston, concluded that there was no way that clinical researchers could have predicted FIAU's toxicity. "This was an unexpected, sudden tragedy," Swartz says. "The researchers did everything they could to protect the lives of these patients."

In contrast to the findings of the IOM panel, the FDA report contended that the researchers had committed "serious violations" of federal rules governing clinical trials. The IOM committee also disagreed with FDA's call for considering all adverse health events reported in experimental drug trials as related to the drugs themselves. Such a provision, the IOM experts argued, could sharply increase the number of drugs abandoned early in the development process that, with further testing and development, could prove to be both safe and effective.

Seema Kumar

Stephen Straus

Acknowledging that probably nothing could have averted the tragic outcome of the FIAU trial, the IOM report goes on to suggest some changes in the regulation of drug trials. The recommendations include:

- Using independent monitoring and control groups in trials where adverse reactions could be confused with the progression of the underlying disease or the therapy's effectiveness.
- Establishing a no-fault compensation system for research-related injuries.
- Monitoring patients in trials of nucleoside-analog drugs, like FIAU, for six months after the trial ends.
- Analyzing data as it becomes available rather than waiting for all case reports on patients to be completed.
- Conducting more animal and other nonhuman tests to learn more about how nucleoside analogs affect cells.

"The IOM offered balanced and well-reasoned suggestions regarding modifications to clinical research that would further ensure its safety," Straus says. "I, for one, favor adoption of their recommendation for a national mechanism of compensating subjects for injuries that arise during research."

Although the patients and families in the trial, along with Hoofnagle, Straus, and their colleagues, were at the epicenter of the FIAU tragedy, the patient deaths and ensuing investigations also sent ripples of apprehension through clinical research centers everywhere. Consequently, Associate Director for Clinical Research John Gallin says that every NIH investigator should take heart in the IOM panel's conclusions that appropriate procedures were followed in the FIAU intramural trial and that patients received medical care "equal to or above prevailing standards."

> "THE RESEARCHERS DID EVERYTHING THEY COULD TO PROTECT THE LIVES OF THESE PATIENTS."
>
> — MORTON SWARTZ, CHAIR OF IOM PANEL

In fact, when all is said and done, the painful lessons from the FIAU trial may actually serve to strengthen the clinical research community as a whole. As Straus observes: "The cumulative impact of the IOM report and last year's report of the Director's Advisory Committee investigation of the fialuridine studies can only serve to restore confidence that clinical research is a valued national priority and that investigators need not fear that their actions be held to unattainable standards." ■

PROTEIN EXPRESSION LAB: ON THE MOVE IN MORE WAYS THAN ONE

by Rebecca Kolberg

As members of the Protein Expression Laboratory (PEL) can attest, when it comes to intramural research at NIH, movement may not necessarily mean packing up your bags and physically moving to another spot. By this fall, PEL should have a new administrative home, some much-needed new staff, and some new avenues of scientific exploration.

Since it opened in August 1990, PEL has operated under the Office of the Director, charged with producing recombinant human immunodeficiency virus (HIV) proteins and related proteins needed by intramural scientists. However, because OD lacks authority and personnel mechanisms to train biomedical researchers, PEL has not been able to bring aboard scientific staffers crucial to the function of most NIH labs: postdocs.

To solve this problem, and to get PEL into a more simpatico intellectual and administrative home, plans are now in motion to move PEL from OD to NIAMS. After reviewing a number of proposals from several intramural programs, Deputy Director for Intramural Research Michael Gottesman decided that the NIAMS proposal was most likely to ensure PEL's continued service to the NIH community. Currently, the OD and NIAMS are negotiating a memorandum of understanding guaranteeing that PEL will remain a resource for all intramural researchers. Other factors entering into the choice of NIAMS as PEL's new home were the lab's proximity to NIAMS labs in Building 6, the desire to strengthen NIAMS' intramural research presence, and the synergy of PEL with research programs within NIAMS.

Many NIH scientists who concentrate on HIV-related research value the resources and services provided by PEL, which is headed by Paul Wingfield and Stephen Stahl. The protein "factory," which keeps small amounts of a half-dozen or so HIV proteins in its freezer, is capable of churning out up to 1 g of protein with its *Escherichia coli* expression system. However, if the HIV protein in question is readily available commercially, such as HIV-1 protease, PEL prefers to steer researchers to the appropriate supplier through the NIH AIDS Research and Reference Reagent Program Catalog run by the Office of AIDS Research.

RNase H domain of HIV-1 reverse transcriptase.
Summary of ^{15}N relaxation data analysis superimposed on the crystal structure. PEL's Stephen Stahl and Paul Wingfield collaborated with NIDDK researchers on this work. [Reprinted with permission from R. Powers et al., Biochemistry **31**, *39 (1992).]*

Supplying the proteins and expertise needed to meet intramural research demands has kept PEL's six-person staff more than busy over the past five years. Prominent intramural groups, including those headed by Angela Gronenborn, Marius Clore, and Ad Bax of NIDDK and Alasdair Steven of NIAMS, have relied heavily on recombinant proteins produced, purified, and characterized by PEL for X-ray crystallography and high-resolution nuclear magnetic resonance (NMR) spectroscopy studies of potential targets for HIV therapies or vaccines.

But other intramural researchers — whose work only occasionally or tangentially relates to HIV — may not be aware that PEL researchers not only make HIV proteins, but also make "house calls" providing scientists with consultation on the expression and purification of recombinant HIV and related proteins within their own labs.

Projects to which PEL collaborators have made substantial contributions have addressed a wide range of scientific questions. "They [PEL scientists] have almost a preternatural ability to advance a large number of projects simultaneously," says Steven, chief of the Laboratory of Structural Biology at NIAMS.

Since 1990, Wingfield, Stahl, and their colleagues have played an instrumental role in the purification, characterization, and analysis — using innovative ^{15}N relaxation NMR spectroscopy measurements — of the ribonuclease H domain of HIV-1 reverse transcriptase. Wingfield, the laboratory's chief and its expert on protein structure, co-authored a study with Clore and Gronenborn published in the May 21, 1993, issue of *Science* on the kinetics of the folding of the large, all-beta sheet protein, interleukin-1β — considered to be one of the most difficult protein-folding problems solved to date.

Stahl, head of the lab's molecular biology section, soon followed suit, co-authoring a paper with Clore and Gronenborn in the July 23, 1993, issue of *Science* that details the NMR structure of a complex between the DNA-binding domain of the chicken erythroid transcription factor GATA-1 and its target DNA.

Currently, in keeping with its traditional HIV focus, PEL is assisting Ad Bax's group at NIDDK in the search for potential structural partners that may help to stabilize the HIV nef protein. Meanwhile, on an exciting front that appears unrelated to HIV at first glance, PEL researchers are collaborating with NIAMS' Adam Zlotnick in efforts to delineate the apparently unique structure of a protein that coats the nucleus of the hepatitis B virus (HBV). The structure of most viral nucleocapsid proteins consists primarily of beta sheets arranged in a "jelly roll" formation. However, preliminary findings indicate that the HBV nucleocapsid protein, HBcAG, contains many alpha helixes arranged in a non-jelly roll fashion, Wingfield says. There are also intriguing early leads indicating that an HIV nucleocapsid protein, p27, may possess a structure similar to HBcAG's, he adds.

Intramural researchers who have come to rely on PEL for their HIV protein needs shouldn't lose any sleep worrying about the lab's impending move out of OD and into NIAMS, Wingfield says. In fact, he says the addition of a couple of postdocs could enhance PEL's ability to provide both proteins and protein-expression expertise to the NIH community. "I think this is an excellent move. It will make PEL a more settled part of the NIH family as a research group," says Steven.

Although the addition of PEL will definitely be a boon to the research capacity of a small and growing institute like NIAMS, Steven says he's certain that the lab "will continue to be polyvalent in terms of its scientific interactions, and will continue to collaborate on a campus-wide basis."

"OTHER RESEARCHERS CAN HELP US BY LETTING US KNOW ABOUT THEIR INTERESTING IDEAS ON PROTEIN EXPRESSION OR INSIGHTS ON THE STRUCTURE OR FUNCTION OF HIV PROTEINS."

PEL's leaders also have a few nonadministrative changes up their scientific sleeves. The lab has recently extended its activities into protein crystallization in order to advance its interest in structure-function studies. "We feel if we can make the crystals ourselves, it will be more efficient than if we just hand the proteins out to people who may not have our understanding of the proteins," Wingfield says. "It's a routine part of our job to understand the properties and behaviors of the proteins we make."

With the arrival of its long-awaited postdocs, PEL may begin exploring new systems for the expression of proteins that undergo posttranslational modification. Although *E. coli* works well as a system in which large quantities of recombinant proteins can be produced, it lacks the factors necessary to perform the appropriate glycosylation, folding, and other posttranslational modifications required to make many proteins biologically active. One possible alternative may be a system in which genes are inserted via baculovirus and expressed in insect cells, Wingfield says.

Another problem that PEL is working on in collaboration with Norman Walts of NIAMS centers on the rather unruly behavior of some HIV proteins during handling and purification. Take the example of the HIV rev protein, which tends to polymerize into fibers that do not produce good mapping data under standard X-ray crystallography. Rather than fight rev's natural resistance to crystallization, PEL is now trying to chart rev's structure via X-ray diffraction of the polymerized fibers — an innovative technique that has been used to plot the structure of the tobacco mosaic virus at high resolution.

Finally, Wingfield is also trying to wean the intramural research community away from simply viewing PEL as a one-way street that delivers much-needed proteins to their labs. Instead, he wants scientists to regard PEL as a two-way street for the exchange of information on protein expression at NIH. "Other researchers can help us by letting us know about their interesting ideas on protein expression or new insights on the structure or function of HIV proteins," he says. ■

PEL at a Glance

Senior Investigators:
Paul Wingfield, lab chief, expert on protein structure-function.

Stephen Stahl, head of molecular biology section, expert on recombinant-DNA techniques and protein expression systems.

Phone: 402-0940.

Location: Building 6B, Room 1B130.

Resources: This laboratory supplies HIV proteins that are not readily available from commercial suppliers to intramural scientists for collaborative studies. It also provides consultation and help on the expression and purification of recombinant proteins and assists investigators involved in such projects. ■

A SLPI DEFENSE AGAINST HIV

Over the past decade, the absence of epidemiological evidence for adult oral transmission of HIV-1 has intrigued investigators. Initially overlooked was the possibility that the host has, in its defensive repertoire, mechanisms to stave off oral retroviral invasion. The near absence of orally transmitted HIV-1 — like the failure of some individuals to become infected despite repeated exposure to the virus and the emerging profile of seropositive long-term survivors and nonprogressors (1,2) — may provide us with several important opportunities to pursue and identify endogenous host mechanisms of defense against retroviruses. Within the oral cavity, a small endogenous protein may be one source of this antiviral defense, which may account, at least in part, for protection against HIV-1 shed into the oral cavity or acquired through oral exposure (3). Because AIDS is considered to be primarily a mucosally transmitted disease, this mucosa-specific inhibitor may contribute to an initial line of defense.

More than 20 years ago, a low-molecular-weight proteinase inhibitor was described in bronchial secretions (4) and named antileukoprotease (ALP) because of its ability to inhibit granulocyte proteinases (5). Similar serine proteinase inhibitors were subsequently found in other mucous secretions, including those of salivary glands (6,7). Given the widespread distribution of this antiprotease in mucosal fluids and its elastin-protecting capacity, researchers considered its primary role to be protection of the parenchyma against leukocyte proteolytic attack.

In 1986, Robert Thompson of Synergen and Kjell Ohlsson of the University of Lund, Sweden, purified this protease inhibitor from large volumes of parotid secretions, and the newly sequenced protein was dubbed secretory leukocyte protease inhibitor (SLPI) (8). Once SLPI's amino acid sequence was known, various protease inhibitors identified at other mucosal surfaces were found to be identical to the nonglycosylated polypeptide with a molecular weight of 12 kDa and an isoelectric point (pI) greater than 9 (8). The protein, shaped like a boomerang (9), consists of two homologous cysteine-rich domains of 53 and 54 amino acids, which are encoded on separate exons (10). Produced by cells of mucosal surfaces, SLPI is a potent inhibitor of human neutrophil elastase and cathepsin G, and it also inhibits other serine proteases, such as trypsin and chymotrypsin. The recombinant protein (rSLPI), produced in *Escherichia coli*, has the same amino acid sequence, composition, and activity as the native molecule. Researchers at Synergen have shown by site-directed mutagenesis that residue Leu-72 within the COOH-terminal domain is the active site for inhibition of leukocyte elastase and cathepsin G, as well as of chymotrypsin and trypsin (11). The NH_2-terminal domain stabilizes and enhances the activity of the protease-inhibitor complex (12).

PRODUCED BY CELLS OF MUCOSAL SURFACES, SLPI IS A POTENT INHIBITOR OF HUMAN NEUTROPHIL ELASTASE AND CATHEPSIN G, AND IT ALSO INHIBITS OTHER SERINE PROTEASES, SUCH AS TRYPSIN AND CHYMOTRYPSIN.

Five years after the initial purification and sequencing of SLPI, as scientists in our lab were looking for a mysterious HIV-inhibiting fraction that we had isolated from saliva, our path crossed with the path of researchers exploring SLPI's potential as a therapeutic antiprotease in lung disease. Thus, in 1991, we began our experiments in which SLPI was tested and shown to have surprising efficacy at inhibiting HIV-1 infection in vitro. At physiologic concentrations (~1 μg/mL), SLPI inhibits the appearance of reverse transcriptase (RT) activity in human monocyte/macrophage cell cultures exposed to HIV-1 (3). Although the mechanism has not been fully deciphered, the SLPI inhibition is remarkably long-lasting: a single one-hour SLPI treatment at the time of infection suppresses RT activity through several weeks of culture. In addition to inhibiting HIV in monocytes, SLPI inhibits infection of T cells and T-cell lines by laboratory and clinical HIV isolates (3, T.B. McNeely, S.P. Eisenberg, D. Dripps, and S.M. Wahl, unpublished observations).

Another key observation we made in vitro was that cells pretreated with SLPI and washed prior to exposure to HIV-1 were still protected, whereas pretreatment of the virus with SLPI was not inhibitory. This observation has led us to hypothesize that SLPI inhibits HIV by acting on some target in or on the cell — not the virus. This hypothesis was supported by our inability to demonstrate any interaction between SLPI and purified viral components, including gp120, gp160, or HIV aspartyl protease. Importantly, if SLPI's inhibition of HIV is, indeed, related to some cellular molecules and processes, these may ultimately provide a more stable target for the design of anti-HIV therapies than the elusive, rapidly mutating virally encoded proteins that form the basis for some current therapies and candidate vaccines, for example.

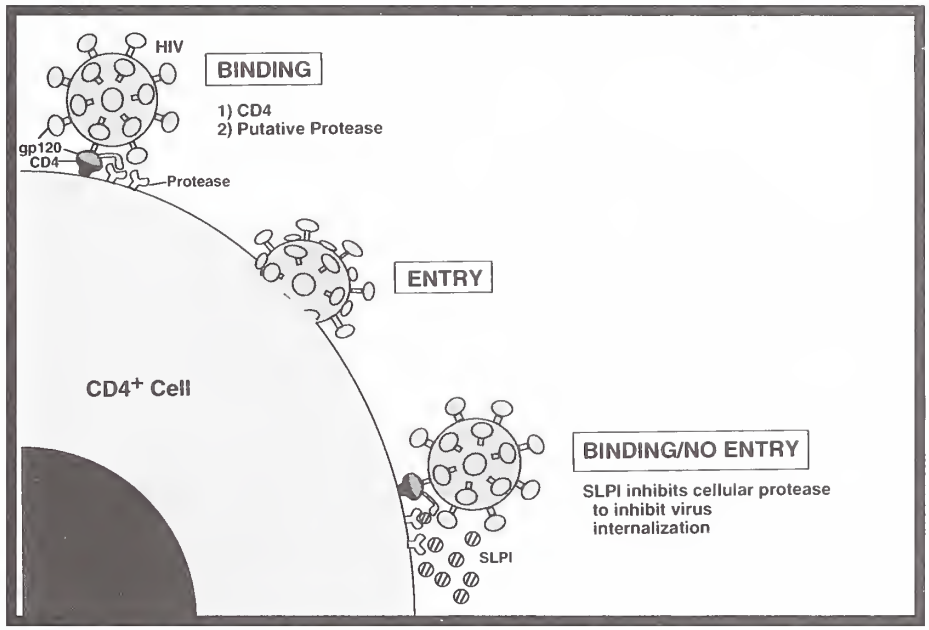
Armed with these in vitro observations, we are trying to piece together a hypothesis of how and when SLPI acts during HIV's infection-replication cycle to foil the virus. As is true for many viruses, HIV replication requires internalization of infectious virions and subsequent utilization of host cellular machinery for the production and assembly of new infectious particles. Antiviral agents that inhibit binding of the virion to the target cell may be removed after initial infection has been averted. On the other hand, compounds such as AZT and R031-8959 that work by disrupting the action of the viral enzymes have no activity during internalization and must be available intracellularly during proviral formation (13) or during the assembly of new infectious particles (14).

Our suspicions are thus that SLPI exerts its anti-HIV activity primarily, although perhaps not exclusively, during internalization. Like recombinant, soluble CD4, a competitive inhibitor of HIV binding, SLPI's inhibitory activity only

by Sharon M. Wahl, Ph.D., Chief, Cellular Immunology Section, Laboratory of Immunology, NIDR; Tessie B. McNeely, Ph.D., Cellular Immunology Section, Laboratory of Immunology, NIDR; and Stephen P. Eisenberg, Ph.D., Synergen Inc., Boulder, Colo.

requires it to be present while the virus attempts to dock on the target cell. Unlike CD4, however, SLPI does not bind viral-coat compounds, but it does bind specifically and with high affinity (1-10 nmol/L) to intact monocytes and to T-cell and monocyte-cell lines (T.B. McNeely, S.P. Eisenberg, D. Dripps, and S.M. Wahl, unpublished observations).

This leads us to the consideration of what cellular components SLPI interacts with to inhibit HIV penetration of the cell, and a few emerging observations from HIV studies have suggested some possibilities. Researchers now believe that HIV binding to CD4 is necessary for penetration of T cells and monocytes but suspect that CD4 binding may not be *sufficient* for viral entry into targeted cells. Nevertheless, attempts to identify an accessory molecule enabling HIV entry have been frustrating and inconclusive. Among the list of candidate accessory molecules are several proteolytic enzymes. These enzymes are considered possible candidates because cleavage of HIV's V3 loop of the envelope glycoprotein gp120 is purported to be necessary for viral internalization (15) and because the loop is readily clipped by several proteases common to the white cell.



A hypothetical SLPI defense against HIV-1. *The binding of the HIV envelope glycoprotein, gp120, to cell-surface CD4 is the initial cellular event in HIV infection. An additional obligate step has been postulated that may involve a proteolytic cleavage of gp120 to facilitate viral entry. SLPI, a serine protease inhibitor, may inhibit this cleavage event to impair viral fusion and/or internalization.*

The possibility that proteolytic cleavage of HIV's coat protein is required after the virus binds to CD4 points to a potential role for SLPI: blocking this cleavage step. Although in vitro studies have demonstrated that two of the proteins SLPI inhibits — elastase and cathepsin G — can cleave gp120 (T.B. McNeely, S.P. Eisenberg, D. Dripps, and S.M. Wahl, unpublished observations), the antiviral effects of SLPI may be a consequence of binding to, or inhibition of, another as-yet-uncharacterized serine proteinase. Possibilities include tryptase TL2 (16) and CD26, a dipeptidyl dipeptidase (17), which have been suggested as the proteases responsible for cleaving the V3 loop, but SLPI does not inhibit the activity of CD26 (S.P. Eisenberg, unpublished observations), and its role in HIV infection is disputed. We are also entertaining the possibilities that SLPI interferes with the fusogenic mechanisms of the HIV envelope glycoprotein (18) or that its inhibition is the direct or indirect result of interference with viral binding or some other type of interaction SLPI may have with the target cells. One intriguing possibility revolves around earlier studies in which SLPI, administered in vivo to sheep, was found to induce glutathione (19). Some other compounds that inhibit HIV, such as *N*-acetyl-l-cysteine and cystamine, do so by increasing glutathione concentration (20,21), and it is conceivable that such a pathway is also triggered by SLPI. At this early juncture in defining SLPI's modus operandi, we must consider that multiple mechanisms may be involved in the antiviral activity until the emerging data force us to conclude otherwise.

Observations on SLPI in vivo are indirect or extremely sketchy at this time. Although very little is known regarding the ability of SLPI to inhibit HIV in vivo, transmission of HIV via the oral cavity remains an extremely rare event, consistent with a mucosal antiviral screen that is specific to the oral cavity. SLPI is present in saliva at fairly high concentrations (~1 µg/mL), and depletion of SLPI from saliva results in a decrease in HIV-1 inhibitory action of saliva (3). In assessing in vivo localization and function of SLPI in HIV^+ and HIV^- individuals, we have detected similar levels of protein expression in salivary glands and in saliva of both groups. Earlier ELISA testing (6) using antibody to what was known 10 years ago as low-molecular-weight inhibitor (LMI) — probably SLPI — showed that the inhibitor's concentrations were high in saliva, tears, bronchial fluids, and cervical secretions; and lower in seminal fluid. Both blood serum and rectal fluid contain LMI levels as much as 1,000-fold lower than those found in other mucosal secretions — levels that are below the minimal concentration required for in vitro antiviral

continued on page 22.

The Interest Group Gazette

Something Old...

The mass spectrometry community at NIH is fortunate to have a couple of avenues, including one that's been around for two decades, for informally exchanging ideas with area researchers who share similar interests. The first is a bimonthly **mass spectrometry journal club** that meets at 10:30 a.m. on alternate Thursdays in Building 10, Room 7N101. For more information on the journal club, contact Lewis Pannell (phone: 402-2196; e-mail: lkp@sx102a.niddk.nih.gov). The second option is the **Mass Spectrometry Discussion Group of the Greater Washington/Baltimore Area,** an interest group with a 20-year history. The meetings are usually jointly led by scientists, many with protein-biomolecule research interests, from NIH, the National Institute of Standards and Technology, the Naval Research Laboratory, Johns Hopkins University, and the University of Maryland - Baltimore County. For more information, contact John Callahan (Analytical Chemistry/Code 6113, Naval Research Laboratory, Washington, DC 20375; e-mail: Callahan@NRLFS1.nrl.navy.mil; phone: 202 767-0719; fax: 202 404-8119).

Although it, too, has been meeting for many years, the **NIH Epidemiology Interest Group** has only recently gotten around to making its presence official by registering with the Office of the Deputy Director for Intramural Research. The group's goals are to provide NIH's broad and diverse community of scientists in epidemiology, biostatistics, and related fields with a means for

- exchanging experiences and discussing research-related, professional, and administrative topics of mutual interest,
- keeping abreast of their colleagues' latest research findings and methodological developments,
- building a stronger alliance for responding to inter-institute issues regarding epidemiology,
- interacting with distinguished epidemiologists from outside NIH, and
- drawing attention to epidemiology's significant contributions to recent advances in medical knowledge.

The monthly sessions are open to anyone interested in epidemiology or in the particular topic of discussion. Meeting dates and locations are posted in the NIH Calendar of Events. Sessions are usually scheduled for the third Wednesday of each month, 3:30 - 5:00 p.m., in Building 31 or in the Executive Plaza North conference rooms. To discuss ideas for future activities, contact the chair of the interest group, Richard Havlik, associate director of NIA's Epidemiology, Demography, and Biometry Program (phone: 496-1178; fax: 496-4006). To join the group, send your name, ICD, address, phone, and fax to Martina Vogel (mail: Federal Building, Room 6C-10; phone: 496-6614; fax: 402-0420; e-mail: MartinaV@nih.gov).

... and Something New

The recently formed **Inter-Institute Interest Group on Bioinstrumentation** has decided to hold its meetings on the first Tuesday of each month at 2 p.m. in Building 13, Room 3W54. The purpose of the group is mutual education of NIH scientists interested in the science and technology of bioinstrumentation. Anyone is welcome, but the group particularly seeks members who want to improve the state of the art by designing or modifying their own instruments. Organizers expect to have tutorials and brainstorming sessions on particular topics, as well as occasional outside speakers. For more information, contact Steve Leighton (phone: 496-4426; e-mail: leighton@helix.nih.gov).

Another relative newcomer to the interest group scene is dedicated to promoting the exchange of information on the intracellular trafficking of macromolecules. The **Protein Trafficking Interest Group** held its first meeting March 14. After the organizational meeting, Jennifer Lippincott-Schwartz of NICHD spoke on "The Mechanism of Golgi Dispersal during Microtubule Disruption." The group decided to hold its workshops on the second Tuesday of each month from 3:30 - 5:00 p.m. in Building 10, Room 9S-235 (Bunim Room). Members of participating labs will speak about their research on a rotating basis. Topics to be discussed include the mechanisms of macromolecular sorting, membrane fusion, the regulation of vesicular traffic, antigen presentation, organelle biogenesis, and membrane-cytoskeleton interactions. All members of the intramural community, as well as scientists from area universities, are welcome to participate. For more information, contact Harris Bernstein (phone: 402-4770; e-mail: bernsteh@ncifcrf.gov) or Sam Cushman (phone: 496-5953; email: samc@bdg10.niddk.nih.gov).

Meanwhile, the **NIH-wide Motility Interest Group**, formed to bring together intramural researchers studying how cells and the molecules and organelles within cells move, is off to an impressive start. About 80 people gathered in Building 10's Bunim Room in January to hear Edward Korn of NHLBI discuss "Amoeba Myosins: Structure, Regulation and Cell Function." This interest group wants to foster fruitful interactions among the many intramural scientists who use a variety of techniques and approaches to study cell motility in different systems and at different levels of organization. For more information contact Robert Horowits (phone: 402-1917; e-mail: horowits@helix.nih.gov).

Researchers who are interested in nerve-muscle interactions are also getting an interest group of their very own. The **Nerve-Muscle Interest Group at NIH** plans to meet every second Wednesday at 8:30 a.m. for informal presentations of ongoing work and discussions of topics or techniques of general interest to the group. For more information, contact Matt Daniels (phone: 496-2898; e-mail: mdaniels@codon.nih.gov) or Evelyn Ralston (phone: 496-1296; e-mail: esr@codon.nih.gov).

And last but not least, a **Gene Therapy Interest Group** is starting to take shape. The group, which is open to all NIH staffers with an interest in gene-transfer technology and potential clinical applications of gene therapy, will hold its meetings in Lipsett Auditorium from noon to 1 p.m. on the second and fourth Tuesdays of each month. Organizers expect to alternate presentations by intramural investigators, with talks by outside speakers on particularly hot topics. For more information, contact Michael Blaese (phone: 496-5396; e-mail: mblaese@nchgr.nih.gov). ■

Digitized Images: From the Clinic to Your Desktop

by Joseph A. Frank, M.D., OD; Ronald Levin, Sc.D., NCRR; Margaret Douglas, DCRT; and Geoff Sobering, Ph.D., Pulsar Corp.

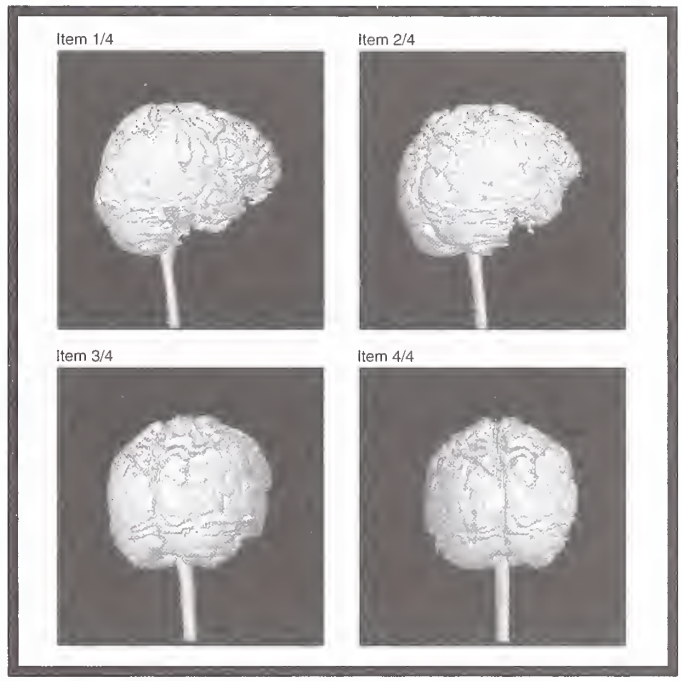
We read with great interest Dr. Gallin's recent editorial in *The NIH Catalyst* (November-December 1994), in which he mentioned that digitized images such as X-rays will soon be available on desktop computers in the Clinical Center. With our Multimodality Radiology Image Processing System (MRIPS) recently coming on line, Dr. Gallin's vision of having images displayed on a researcher's desktop computer has become a reality.

Since mid-February, MRIPS has been capturing all images from NIH's General Electric and Picker magnetic resonance (MR) and computerized tomography (CT) scanners without operator intervention. We are also poised to automatically capture images from the NIH MIRAGe system at the Clinical Center's Nuclear Medicine (NM) and Positron Emission Tomography (PET) departments.

Within an hour after completion of an MR or CT exam, the images, including the header descriptive information, are available to a researcher via the MRIPS Data Registry. Access to data on the MRIPS servers is protected by multiple levels of security. Only researchers with authorization from their clinical director may access clinical examinations. At the researcher's request, data access may be restricted to the principal investigator or the principal investigator's work group. Beyond those levels of security, the data are secured with password protection.

Retrieval of these images is possible from either UNIX workstations (HP, DEC, SUN, and SGI) or Macintosh or PC systems that support a local X-windows server. The images from CT, MRI, or NM/PET can be viewed and analyzed by any of the many image processing software packages supported by MRIPS. These packages, which are available to researchers at no additional cost, include MEDx, Analyze, IDL, and PV-Wave. Once access is granted by the MRIPS Data Registry, a data set may be read, viewed, and analyzed using NIH's Image version 1.57 software on any Macintosh via the AFP/AFS (AppleTalk Filing Protocol/Andrew File System) Translator maintained by MRIPS. Because MRIPS is supported by the management fund, individual researchers are not charged for the costs of disk space on the MRIPS file servers.

The MRIPS data registry greatly facilitates access to clinical images, conversion of images from one format to another, and simultaneous analysis of 3-D volumes of images from multiple modalities. The software package MEDx, designed for MRIPS specifically for the NIH clinical-imaging research community, includes several well-known algorithms used for brain registration, including the Chen/Pelizzari algorithm. This has been particularly useful in the registration of MRI to PET data, and for functional MRI studies of high-resolution anatomical images.



The MEDx toolbox is available to any member of the NIH intramural community. MEDx can be run on your Advanced Laboratory Workstation (ALW) by executing the command /afs/.nih/od/MRIPS/bin/medx. MEDx was created to handle large imaging data files (e.g., 200- to 500-megabyte data sets obtained with functional MRI). Therefore, to run MEDx efficiently on your workstation, you need the following configuration: 1) at least 64 megabytes (preferably 128 megabytes) of physical random-access memory (RAM), 2) preferably two 1-gigabyte disks, one for UNIX and one for the AFS cache, and 3) both a shared memory kernel (with at least 32 segments and 32 megabytes per segment) and a shared memory X-server should be activated on the workstation. To get the shared memory resources activated on the ALW, submit a problem trouble report, or "ptr," asking for a "MEDx" kernel. In the ptr, please tell the ALW support staff the amount of physical memory and the type of graphics card installed on the workstation.

In response to the overwhelming storage demands of the imaging community, MRIPS in the future plans to expand magnetic disk storage to about one terabyte. This increase should allow storage of all CT, MRI, and PET data obtained in the Clinical Center over the course of a year. MRIPS servers are already using a high-speed, 100-megabyte/sec FDDI (fiber optic) network and are fully forward compatible with future development of high-speed data and video transmission, such as asynchronous transfer mode (ATM).

For more information, contact MRIPS support staff (phone: 402-6000; e-mail: medxbugs@list.nih.gov). There is also a MRIPS tutorial every Friday at 12:30 p.m. in the Laboratory of Diagnostic Radiology Research, Building 10, Room B1N256. A summary of the weekly tutorials and details about MRIPS may also be obtained from the MRIPS World Wide Web server (http://www-mrips.od.nih.gov/). ■

Science and The World Wide Web: A Poster Challenge

These days, it's almost impossible to be a cutting-edge biomedical researcher without at least testing the waters of international computer networking via the Internet. And the part of the Internet where the surf's really up for science is the World Wide Web, often referred to simply as the Web. In this Hot Methods Clinic, we run down the basics of navigating the Web for those of us who are still standing on the shore — and we issue a challenge to everyone at NIH from cyber-novices to seasoned pros: roll up your sleeves and help us create the first NIH Scientific Poster Conference on the World Wide Web.

The Web And How It Works

The World Wide Web is the most user-friendly and unique part of the Internet because of the way in which information is presented and connected. Text, image, sound, and video information is stored in what is called a Web page. Web pages reside in the memories of computer servers connected to the Internet, and every Web page has an address, called a uniform resource locator (URL), that anyone can access with the help of computer programs called Web browsers. An important facet of the Web is that each Web page can reference any number of other Web pages, just as a scientific article can reference other scientific papers. Retrieving a referenced Web page is as easy as pointing your cursor at highlighted words or images, called hyperlinks or anchors, and then clicking on them with your mouse. This ease of information retrieval, commonly referred to as Web browsing or Web surfing, is at the heart of the usefulness of the World Wide Web. The kinds of information available on the Web span from the trivial to the serious, from the commercial to the educational. You can find a collection of paintings from the Louvre, as well as shopping "malls," CIA satellite photos, and DNA and sequence-structure protein databases. For example, the following scenario could be taking place anywhere at NIH today.

A researcher sits down at her computer. She clicks on the icon of a World Wide Web browser and is connected to the Web. Her eyes are greeted by pages full of color pictures and text. Blue highlighting indicates the words, phrases, and pictures containing hyperlinks to other Web documents. With several clicks of the mouse, she can scan the current weather map and then take a peek at the seven-day forecast.

More clicking. This time, the scientist's screen is filled with a list of subjects from the World Wide Web Library Catalog, which references over 100,000 Web pages. All of the subjects are highlighted in blue, meaning a single click with the mouse will retrieve that information and bring it effortlessly to the screen.

She clicks on "Biotechnology" and then on a few more highlighted words and arrives at Johns Hopkins University BioInformatics Web Server. She clicks on the highlighted GenQuest. She sets her search parameters and enters the DNA nucleotide sequence of a candidate gene that she has cloned. Somewhere in Baltimore the entire on-line Genome Sequence Database is rapidly searched. An answer to her query is returned in a few minutes, containing all sequences that match her search parameters. She then enters NRL 3D — the sequence-structure protein database Web page — and compares the structure of the protein predicted to be encoded by her new gene with the structures in the database. She saves the location of the page for quick future reference with an electronic bookmark.

The technology behind the Web is developing at a phenomenal pace. Computers are able to handle more complex data at faster rates, and new and faster computer communication methods, such as fiber optics, digital satellite links, and compression algorithms, are being developed. So much development is occurring on the Web that in just a few years, an NIH researcher might enter the following in his diary.

I was able to e-mail out the current draft of my paper to the co-authors. The transfer took a little long, all of two seconds; either we have too many figures or everyone is on remote from home today — my guess is the latter. They should be able to send back the corrections later today so that it can get published on the Web tomorrow.

My virtual assistant found five articles this morning that I may be interested in reading and has found a possible binding site for my protein on the structural protein database. I'll get to them tonight on my laptop via the digital satellite network.

My video presentation at the Virtual Scientific Meeting went well enough. Our department has a few good posters on-line. I did a little bit of browsing through other team's posters, asked a few ques-

A Web Sampler

Some interesting and useful Web locations are listed below:

NIH Home Page:	http://www.nih.gov/
NIH Campus Yeast Interest Group:	http://www.nih.gov/sigs/yeast/index.html
JHU BioInformatics:	http://www.gdb.org/hopkins.html
Hubble Space Telescope:	http://stsci.edu/top.html
Internet Music Archive:	http://sunsite.unc.edu/ianc/
Paleolithic cave drawings:	http://www.culture.fr/culture/gvpda-en.html
WebCrawler search:	http://www.biotech.washington.edu/WebCrawler/WebQuery.html

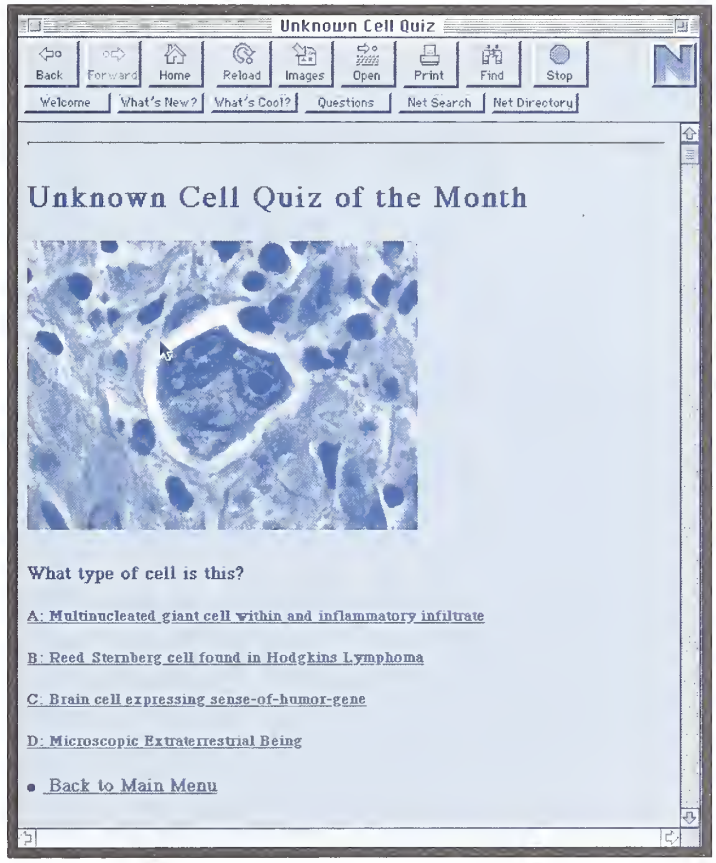
by Lance A. Liotta, M.D., Ph.D., NCI; Vivian Norman, NCI; and Alex Lash, M.D., NCI

tions, attended a few on-line lectures, and met a few potential collaborators.

Protocol

What do you need to start exploring the Web? First, you must have a Macintosh computer [68020 processor or later with 4 megabytes (MB) of random-access memory (RAM) running system 7 or later], or an IBM computer or clone [386 processor or later with 4 MB of RAM running Windows]. You will also need a direct Internet connection. Information on how to get such a connection is available through your Local Area Network (LAN) administrator. The name of this person is available through DCRT (594-3278). Finally, you must get a program called a Web browser. Examples of Web browsers are Netscape, by Netscape Communications Corp. of Mountain View, Calif., and Mosaic, by the National Center for Supercomputing Applications (NCSA) at the University of Illinois in Urbana-Champaign. The programs or instructions on getting them are available through PubNet, which is a collection of software that is accessible when your LAN connection is made. Mosaic is free for educational use, and there is a $39 licensing fee for Netscape. Some Macintosh and Windows versions of Web browsers are also bundled with manuals and are available at many bookstores for the price of the book alone. Bear in mind that mention of a specific product in "Hot Methods Clinic" does not constitute an endorsement.

Once you have these three necessities — a suitable computer, an Internet connection, and a browsing program — you are ready to surf the Web. Click on the Mosaic or Netscape icon to get it running. The NCSA or Netscape "home" page, or initial directory page, will automatically be displayed. You can point and click on any words or images highlighted in blue or other contrasting colors to move through Webspace. To access a Web page for which you have the address, open the "File" menu item and choose either "Open location" in Netscape or "Open URL" in Mosaic. A dialog box will appear, in which you should enter the Web address and click on "OK" or hit return. A sample Web page, of NCI's Laboratory of Pathology's Unknown Cell Quiz, appears in Figure 1. Its Web location (or address) is: http://www.clark.net/pub/ nih/pathlab.html.



A sample Web page. *This "Unknown Cell Quiz" is just one part of the scientific "fun and games" accessible through NCI Laboratory of Pathology's home page, which is located at: http://www.clark.net/pub/nih/pathlab.html*

Creating your own Web pages requires knowledge of the Hypertext Mark-up Language (HTML) and a text-editor program, but specialized editing programs are available for free at several Web locations. The easiest way to find a copy is to search the Internet for the name of a specific program using a search algorithm, many of which are quickly accessible via the Net Search button in Netscape.

NIH Scientific Poster Conference Page

Many analogs to Internet's electronic world can be found in our physical world: the Web is similar to a marvelously large library packed with books, videotapes, and recordings; and e-mail resembles regular mail service or fax transmission in that it delivers written communications, except that it does the job faster. The Internet in general, and the Web in particular, promises to turn more of our physical activities into electronic activities. Instead of wasting valuable research time traveling to distant locations to attend scientific meetings, we may be able to attend "virtual meetings" by taking just a few steps to computers in our labs or in our homes. Instead of waiting for scientific journals to wend their way through the printing process and the postal system, on-line journals might deliver the hottest new articles, figures and even supporting videos straight to our desktop computers — allowing us to whip back our comments on the research to the authors or the editors in a flash via e-mail. Then there's the very real possibility of virtual assistants — computer programs that perform routine, arduous tasks for their supervising scientist, such as continuously searching scientific literature and databases for articles or entries specific to a given research interest.

continued on page 23.

FOGARTY SCHOLARS-IN-RESIDENCE UPDATE: A NEW CLINICAL FOCUS

by Jack Schmidt, Ph.D.

The Fogarty International Center's Scholars-in-Residence Program has brought more than 200 internationally renowned biomedical researchers to NIH over the past 26 years, yet somehow very few of these scientists have been clinicians. Recognizing that NIH's clinical investigators have as much to gain from interacting with their distinguished peers from around the globe as do basic scientists, Fogarty International Center (FIC) Director Philip Schambra and Clinical Center Director John Gallin are launching a special initiative this year to solicit nominations of outstanding clinical researchers for the Scholars-in-Residence Program. As participants in the program, clinical scholars would make regular rounds on the Clinical Center wards, take part in conferences, hold seminars, and write scholarly articles or conduct research that complements existing clinical programs.

Normally, FIC scholars' appointments run for 12 months, which may be divided into shorter terms of at least three months in length. However, because some clinicians may find it logistically difficult to spend an extended period of time at NIH, FIC will allow them to shorten their appointment terms to three months total. The first round of nominations for the clinical scholars initiative closed April 1, and candidates who are selected are expected to arrive at NIH during fiscal year 1996. Meanwhile, the following Fogarty scholars who were nominated previously are set to begin or resume their NIH residence during the next few months.

Lev Bergelson *to 10/24/95*
Formerly a professor of biochemistry at the Shemayakin Institute of Bioorganic Chemistry in Moscow, Bergelson is now a professor of biochemistry at Hebrew University of Jerusalem. He is recognized worldwide for his research on the structure and function of lipids in biological membranes, the role of glycolipids in immunomodulation, and the pathogenesis of cardiovascular disease. Recently, his studies of the involvement of lipids in ligand-receptor interactions resulted in the development of a new method for quantifying cell-antibody reactions. Bergelson was nominated by Adrian Parsegian, DCRT.

Yadin Dudai *to 8/31/95*
A professor of neurobiology and dean of the biology faculty at the Weizmann Institute of Science, Rehovot, Israel, Dudai has made important contributions to the understanding of the genetic and biochemical bases of learning and memory. His demonstration of the involvement of adenyl cyclase and other second-messenger components in short- and intermediate-term memory has proven particularly important. His book, *The Neurobiology of Memory*, has become a standard reference in the field. Dudai was nominated by Mortimer Mishkin, NIMH.

Benjamin Geiger *to 9/30/95*
Dean of the Feinberg Graduate School and a professor in the Chemical Immunology Department at the Weizmann Institute of Science, Geiger has made major contributions to cell biology, especially elucidating the structure and function of the cytoskeleton and exploring the importance of cell adhesion. His characterizations of important cytoskeletal molecules, such as vinculin and α-actinin, and his research on cell-cell contacts and cell-extracellular matrix interactions have been fundamental to our understanding of cell growth, differentiation, and metabolism. Geiger was nominated by Ken Yamada, NIDR.

Illana Gozes *to 8/31/95*
Chair of the Chemical Pathology Department at Tel Aviv University in Israel, Gozes is an international authority on vasoactive intestinal peptide (VIP), having cloned the *VIP* gene. Gozes has demonstrated that a VIP antagonist of her own design interferes with cancer cell division and that a lipophilic VIP analog can be used to treat impotence. She has broad experience in identifying and studying the mode of action of neurotrophic growth factors. Gozes was nominated by Douglas Brenneman, NICHD.

Tasuku Honjo *to 9/5/95*
A professor of medical chemistry at Kyoto University in Japan, Honjo is one of the world's leading molecular immunologists. He has done pioneering work on the molecular genetics of immunoglobulin heavy chains and on

How to Nominate A Scholar Candidate

Nominations for the Scholars-in-Residence Program may be made by senior NIH staff members and should be sent to Jack Schmidt, Director, Division of International Advanced Studies, FIC, Building 16, Room 202. For more information, contact Schmidt (phone: 496-4161; fax: 496-8496; e-mail: ujs@cu.nih.gov). The nomination package should include

- a letter describing the candidate's contributions to research and his or her potential to interact meaningfully with NIH scientists,
- a curriculum vita and bibliography of the candidate, and
- names and addresses of at least eight references, including four from outside NIH; FIC will ask the references to evaluate the candidate's qualifications. ■

the mechanism of antibody class switching. He has also contributed greatly to our knowledge of lymphocyte development and function. Honjo's recent interest is in the interrelationship between programmed cell death and autoimmunity. Honjo was nominated by Igor Dawid, NICHD, and William Paul, NIAID.

Koji Kimata *to 8/31/95*
Director of the Institute for Molecular Science of Medicine at Aichi Medical University in Japan, Kimata is renowned for his work on the structure and function of connective-tissue molecules and, in particular, on the role of proteoglycans in cartilage development, cell binding, and growth-factor regulation. His studies have been fundamental to the understanding of the biosynthesis and developmental regulation of extracellular matrices. Kimata was nominated by Yoshihiko Yamada, NIDR.

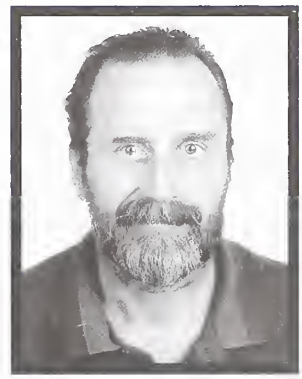
Yuan Chuan Lee *to 10/11/95*
A professor in the Biology Department at Johns Hopkins University in Baltimore, Yuan Chuan Lee has a worldwide reputation in the fields of carbohydrate, glycoprotein, and glycoconjugate biochemistry. He conducted pioneering studies of the structure and specificity of cell-membrane receptors and was a leader in developing much of the technology that led to the current blossoming of glycoconjugate research. Lee was nominated by Hao-Chia Chen, NICHD.

Suryanarayan Ramachandran *to 6/15/96*
Until recently, Ramachandran was secretary of biotechnology in India's Ministry of Science and Technology, responsible for overseeing the biotechnology activities of six governmental agencies in the areas of health, agriculture, and environmental development and safety. As a microbial biochemist, he has broad research experience in the mode of action of antibiotics and in the development of improved technology for the production of antimalarials and antibacterial vaccines. He has gained an international reputation in biotechnology and immunization policy. Ramachandran was nominated by John LaMontagne, NIAID.

Eugene Rosenberg *to 9/30/95*
A professor in the Molecular Microbiology and Biotechnology Department at Tel Aviv University in Israel, Rosenberg is a global leader in research on microbial adherence and ecology and has made many important contributions to basic science and applied microbiology. His work has encompassed studies of polysaccharide biosynthesis and degradation, the biology of mycobacteria, bacterial differentiation, microbial emulsifiers and dispersants, and cell-surface hydrophobicity. He holds many patents in the area of biomaterials and microbiology and has extensive experience in the international biotechnology community. He was nominated by Paul Kolenbrauder, NIDR.

Giancarlo Vecchio *to 9/30/95*
A professor of oncology at the University of Naples Faculty of Medicine in Italy, Vecchio is best known for his research on epithelial carcinogenesis. He is the discoverer of the papillary thyroid carcinoma *(PTC)* oncogene, which is responsible for a high percentage of human thyroid tumors. He has attained international recognition through his work on molecular virology and malignant transformation. Vecchio was nominated by Stuart Aaronson, formerly of NCI. ■

RECENTLY TENURED



John A. Cidlowski *received his Ph.D. from the Medical College of Georgia in Augusta in 1975. In 1978, Cidlowski joined the faculty in the Department of Biochemistry at the University of Vermont in Burlington before becoming a professor of physiology at the University of North Carolina at Chapel Hill in 1982. Cidlowski came to NIEHS in January 1995, where he currently heads the Molecular Endocrinology Group in the Laboratory of Integrative Biology.*

Our laboratory's primary interest is understanding how steroid hormones that are induced by stress — such as glucocorticoids — regulate the growth, differentiation, and death of both immune and nonlymphoid cells.

Currently, we are pursuing three research projects. The first centers on the regulation of apoptosis in normal and neoplastic lymphocytes by steroid hormones and other environmental agents. We are trying to define the effectors of apoptotic pathways, purify the effector proteins, and clone the genes that encode these molecules. Our laboratory has identified one nuclease, called NUC-18, that is strongly implicated as an effector of apoptosis. We hope to complete work on other enzymes soon. We are also interested in the evolution of apoptosis and are currently evaluating this process in yeast, using pulsed-field electrophoresis and yeast strains deficient in NUC-18.

A second focus of our work is elucidating the molecular mechanisms that control the expression and turnover of glucocorticoid receptors during cellular signaling. We have discovered a unique response element within the coding region of the glucocorticoid-receptor gene that is sufficient to account for homologous down-regulation of glucocorticoid receptor by its own ligand. My colleagues and I have also recently characterized the expression and function of a nonligand-binding form of glucocorticoid receptor that has the properties of a dominant, negative repressor.

Finally, we are interested in understanding how environmental molecules, such as nutrients and vitamins, regulate gene expression. Studies in our laboratory have shown that pyridoxal phosphate, the active form of vitamin B_6, profoundly decreases the ability of steroid receptors to transduce signals. The molecular mechanisms responsible for this phenomenon are under investigation. ■

Gender Bias in the Schools: Is Science the Biggest Loser?

by Mary W. Hodges, DCRT

A recent mailing reminding me of my 45th class reunion from the University of Pennsylvania did not exactly stir up fond memories. Instead, it dredged up recollections of the blatant gender bias that deterred me — and my female classmates — from attempting advanced science and math courses during our undergraduate years, even though many of us would have liked to pursue careers in those fields. Although major strides toward reducing gender bias in education have certainly been made since my college days, much still remains to be done, as the following article illustrates.

"If the cure for cancer is forming in the mind of one of our daughters, it is less likely to become a reality than if it is forming in the mind of one of our sons. Until this changes, everybody loses."

Armed with data to back up rhetoric like that, David Sadker, who is a professor of education at The American University in Washington, D.C., is waging a campaign to show how gender bias in the U.S. educational system is depriving our nation of female scientists. In a presentation at NIH on Feb. 6, Sadker outlined results from four years of social science research in hundreds of American classrooms from elementary through graduate schools.

As part of those studies, classroom observers trained by Sadker and his late wife Myra counted and timed situations in which male and female students were called on, praised, disciplined, or given individual assistance. The Sadkers' data showed, for example, that teachers tended to wait at least three times as long for male students to answer — 3 to 5 seconds — as for female students — 0.9 seconds. When female students were allowed the same amount of time to respond as males, they gave more complete responses, more accurate answers, and volunteered more often. This, says Sadker, strengthens self-confidence, which in turn works to encourage females to elect the more advanced math and science courses required by many professional careers.

Lorna Hearlley

Jacqueline Crawley

The Sadkers' recent book, *Failing at Fairness: How America's Schools Cheat Girls* (Simon & Schuster, New York, 1994), also presents a disturbing picture to those looking to expand tomorrow's pool of scientific talent:

"Teachers' beliefs that boys are smarter in mathematics and science begin in the earliest school years, at the very time when girls are getting better grades and equal scores on the standardized tests. Many adults think that boys possess innate mathematical and scientific ability. ... Girls, especially smart girls, learn to underestimate their ability."

"When girls lose their confidence in their ability to learn math and science, they avoid these subjects. When they believe they can't succeed, they become less willing to attempt new science and math tasks. As they have fewer and fewer experiences with math and science, they become less capable. As their competence withers so does their self-esteem, and the vicious, connected cycle continues...."

Interviews with NIH female scientists lend support to many of the Sadkers' hypotheses. For example, despite their generational differences, both Jacqueline Crawley, who heads the Section on Behavioral Neuropharmacology in NIMH's Experimental Therapeutics Branch, who entered college in the 1960s, and postdoc Jennifer McDowell of NIDDK, who entered college in the 1980s, agreed that in their high schools, it "was not cool to be smart" because boys did not like smart girls.

Fear of being socially shunned as a female "brain" is one reason that many girls opt out of advanced math and science courses in the middle and high school years, according to the Sadkers. Such a decision may later block a girl's access to careers in science and technology because she lacks the preparation needed to take college-level courses in those fields.

Lorna Hearlley

Jennifer McDowell

When female intramural researchers were asked what encouraged them to pursue advanced science during their high school years, Crawley and McDowell singled out two main factors. First, their parents encouraged them to view any goal as attainable. Second, starting early in their school years, they were put in an advanced-placement track, where they were grouped with students of comparable abilities and where gender did not matter as much.

Susan Shoaf, a senior staff fellow who is acting chief of the Unit of Pharmacokinetic Studies in NIAA's Laboratory of Clinical Studies, underscores the importance of an instructor's attitudes and actions. "Teachers must emphasize that when it comes to learning, girls can learn anything a boy can. They just sometimes need to learn it differently."

Contact with female scientists and other research-oriented women also helps to cultivate girls' interest in scientific careers. McDowell notes that this need does not disappear when young women enter the lab: "I think we need more role models/mentors — which would mean changes in tenure systems, etc., which make it more possible to combine a career and family."

Although they acknowledge that the gender lines guarding the traditional male domains of mathematics, science, and computer technology are gradually vanishing, the Sadkers caution that "harmful remnants remain."

For example, although today's science textbooks are less sexist than in the past, the Sadkers contend that they remain subtly biased. Their research found that modern texts usu-

Widening the Scientific Circle

The following is a summary of NIH's new "Guidelines on Inclusion of Women, Minorities, and Persons with Disabilities in NIH-Sponsored and/or -Supported Intramural and Extramural Scientific Meetings and Conferences." The guidelines, inspired by a similar effort by the National Science Foundation, took effect March 31 and help to fulfill the diversity requirements of the NIH Revitalization Act.

It is NIH policy that organizers of scientific meetings should make a concerted effort to achieve appropriate representation of women, racial/ethnic minorities, persons with disabilities, and other individuals who have been traditionally underrepresented in science in all NIH-sponsored and/or supported scientific meetings. In addition, organizers who name NIH as a sponsor or use NIH facilities must make a concerted effort to achieve appropriate representation in compliance with this policy. "Appropriate" means representation based on the availability of scientists from these groups known to be working in a particular field of biomedical or behavioral research.

The plans to seek appropriate representation should be specified during selection of organizing committees, speakers, and other invited participants, such as session chairs and panel discussants. In addition, efforts should be made to encourage attendance by women, minorities, and persons with disabilities at all NIH-sponsored and/or -supported scientific meetings as a means of increasing their participation in the particular scientific field. The plans to seek appropriate representation will be included as an evaluation criterion during review of the requests for funding for these meetings.

This policy shall apply to all domestic or international scientific meetings sponsored by and/or receiving support from NIH. "Scientific meetings" include all meetings, conferences, workshops, symposia, seminar series, and lectures that involve planning committees, expenditure of funds, invited participants, and that are nationally or internationally advertised. Such meetings may be initiated by NIH's institute, center, or division (ICD) extramural and intramural programs or by contracts, or they may be investigator-initiated request for grants or cooperative agreements. Reasonable efforts should be made, as well, to fulfill the goal of this policy for single seminars sponsored by NIH laboratories or extramural programs.

NIH's extramural and intramural staff who initiate scientific meetings must comply with this policy. It is the responsibility of the ICD directors to implement this policy. The NIH director wil ensure that all extramural and intramural programs comply with this policy. ■

Facts on File: Resources for Women Scientists

One resource that may come in handy for female scientists, as well as any young women whom they may be mentoring, is a file drawer located behind the reference desk of the NIH Library in Building 10. The Resources for Women Scientists File contains helpful books, articles, and information that can be used or photocopied in the library, but not checked out.

For more information, contact Rosaura Valle or Kathy Carroll (phone: 594-1677). The file is divided into the following sections:

- **Association for Women in Science** — Newsletters and announcements from the national and Bethesda chapters of AWIS.
- **Employment Opportunities** — Jobs and postdoc announcements in academia, industry, and health administration. Reference section on "How to Get a Job."
- **Grants and Fellowships** — Grant and fellowship announcements. Reference section on "How to Write and Get a Grant."
- **Education and Outreach** — Mentoring and conference announcements pertaining to both science and education in general. Programs for women considering a science career.
- **Women's Issues** — Articles about gender differences, family, career, and other topics relevant to women in science. Bibliography.
- **Women in Science** — Articles from journals, magazines, and newspapers.
- **Sexual Harassment and Gender-Based Discrimination** — Information on dealing with such issues. List of Equal Employment Opportunity resources.
- **Books** — Collection includes biographical brochures on female scientists at NIH, a National Science Foundation book on visiting professorships for women researchers, a career guide for women in government, information on the "K" Career Development Awards, and a resource and referral directory for child- and eldercare. ■

ally have a special page, insert, or section on "Women in Science," but female contributions to science are rarely mentioned elsewhere in the books. Such token attributions send the message that women's ideas and work do not share equal footing with men's in respected scientific literature, according to the Sadkers.

Those who question whether females still face significant, gender-based hurdles on the pathway to a research career may want to consider the case of an NIDDK medical technician. The technician, who graduated from an upstate New York college in the 1980s, says she was told by her mother that if she went to college to train for a career, she would be taking jobs away from men.

For a videotape of Sadker's presentation, which was sponsored by the NIH Women Scientist Advisors, the Office of Equal Opportunity, and DCRT, contact the DCRT Information Office (phone: 496-6203, fax: 402-007; e-mail: hodgesm@pop.nih.gov). ■

AN EXIT INTERVIEW: SAMUEL BRODER
continued from page 1.

intramural program, to focus on those areas that really excite the imagination or that an individual really loves at a visceral level, and not to let a day go by without continuing the focus and continuing the commitment.

Q: Do you think it's more difficult for them now than it was for you two decades ago?

Broder: Yes. I think the standards of excellence and the limitations of resources that are now at work introduce enormous stresses for people and enormous uncertainties. That makes me sad.

Q: In what direction do you see NCI heading, and what course should it take?

Broder: Ever since the National Cancer Act was passed, there has been a source of friction, or potential friction, between the director of the NIH and whoever occupies the directorship of the NCI. But I think it is very important for the chain of authority — whether it's the director of NIH, or assistant secretary for health, or whatever — to recognize that the NCI is a formidable asset to the NIH as a whole. It does have some special authorities, but those authorities are formidable assets to the NIH.

The National Cancer Program belongs to the NIH, and much of the revolution in American biotechnology ... was a direct and indirect offshoot of the foundation of the National Cancer Program in the early '70s. And we are still reaping the benefits of that in a number of ways. ... I think the intramural program in the total sense is enjoying a benefit of those decisions that were made in the early '70s. It's very important that NCI be viewed as an asset and not as a problem. ...

It's very important for the director of the NIH to get into the habit of praising and overtly supporting the National Cancer Program. It's something that does not require resources per se, it doesn't require special effort, but it does require a focus, an attention, and a visibility.

NCI serves as a model for enlarging the responsibilities and independence of all the institutes. ... For many years, NCI was uniquely situated to publish its own professional-needs budget ... and, in effect, that responsibility and privilege now has been given to other components. The Office of AIDS Research has such authority now, the NIMH has such an authority. NCI has certain special printing responsibilities, the Office of Cancer Communication has a special mission, the director of NCI by statute has a special cancer-information-dissemination responsibility, and all of that can be a foundation for new opportunities for NIH as a whole.

Q: In the era of government downsizing, is it realistic to expect institutes to move in the direction of greater autonomy as opposed to centralization?

Broder: I think the categorical institute concept was one of the most important, innovative ideas in science administration that ever evolved ... it provides a highly professional core of individuals who are committed to solving a health problem using science and the scientific method. It provides a focus with flexibility around a given disease or set of diseases or problems and at the same time, provides an intuitive line of communication with the public. ...

Many people say that the director of NIH is not a political appointment. Certainly, that is true in many ways because the person who holds that job almost invariably is someone of extremely high character and intellectual development. But there's no way of getting around the simple political reality that in government, if you serve in a position in the executive branch where the position is appointed by the president and subject to Senate confirmation, that's a political position. And there are many examples or potential examples where the political imperatives of the day have an effect and can work at the level of the director of the NIH. And that's why it's very important to preserve the historical diversity and independence and career orientation of the categorical research institutes. ...

If the political variables are completely unpredictable, it's important to have a strong core of career oriented, categorical research institutes and not [to] invest too much authority and to create too many expectations in the Office of the Director of NIH. The fact that the current [director of NIH] is a person of unbelievable credentials does not change what I'm saying. One does not determine the powers of the presidency of the United States on the assumption that the incumbent will always be Thomas Jefferson or Abraham Lincoln ...

Harold Varmus in many ways is an astonishingly gifted person, and we are fortunate to have him at the helm. It is very important in reviewing what authorities one wants to give to the Office of the Director of NIH ... to recognize that Harold Varmus does not have a lifetime appointment. We need to have a system that has appropriate balances, appropriate nonpolitical career orientations, and that is self-sustaining and is not predicated on any one person or personality. ... The categorical institutes and the research institutes that have evolved with time have been a wonderfully successful experiment, and they need to be preserved. Sometimes, when something is so successful and working so smoothly, you take it for granted. That part of the system ain't broke!

> "I DON'T BELIEVE IT IS TRUE FOR EVERY MAJOR POSITION HERE AT THE NIH ... BUT CERTAINLY PRESIDENTIALLY APPOINTED POSITIONS SHOULD HAVE A VOLUNTARY, SELF-IMPOSED TERM LIMIT."

Q: What sort of leader does NCI need now?

Broder: It won't be hard to fill my shoes. There are large numbers of people who are highly qualified ... to come in and take the helm. The major requirement is that the person should burn with a passion to prevent and cure cancer. Once you fulfill that one critical job element, a lot of other things fall into line.

Q: What do you consider your biggest achievement at NIH?

Broder: I'd prefer to let other people judge that. I think the thing I'm happiest with is the ability to balance clinical and basic research in multiple formats — and I think that balance is very important. ... I think that the ability of both basic scientists and clinical researchers to do extremely interesting and important projects and to work together on intellectually risky projects is a wonderful feature of the NIH. It makes this place a very magical place ... this will always be one of the most exciting places in the world to work.

Q: Why did you decide at this point in your career to enter the private sector?

Broder: I've been in the government — the Public Health Service — for 22 years ... I've done this job for six years. I want to stress that I don't think it is true in every case, but there are certain positions in government or in any organization that should have a voluntary term-limit rule. And I believe that director of the National Cancer Institute is one of those positions. I don't believe it is true for every major position here at the NIH ... but certainly presidentially appointed positions should have a voluntary, self-imposed term limit. Maybe four years, five years, six years — something in that ballpark. Anything over six years is probably pushing the envelope.

When you take a high-level position, you need to make a number of serious, difficult, challenging decisions. In order to do the job right, you must, by definition, make some people unhappy. I would be very suspicious if anyone was ever to categorize a high-ranking individual as universally loved. That would imply to me that the individual either was never called upon to make difficult decisions or avoided them, and therefore avoided making anybody unhappy. I think the public good is the preeminent consideration, not a local, parochial good. In order to sharpen the focus and to make difficult decisions doable, there has to be some aspect of limitation. Otherwise, there would be a tendency for individuals to simply use their intellect, use their political skills to essentially survive. ...

After a certain amount of time, a cycle of renewal is very important. It's important for biological systems, and I think a cycle of renewal is important for something like the Cancer Institute.

Q: What will your responsibilities be at Ivax?

Broder: I don't know the specifics until I go down there [Miami] ... but I've been given a wide latitude, many degrees of freedom. ... One of the things that really attracted me [to Ivax] was that it's at a certain size that I think bodes well for its continued existence, but it doesn't have an ensconced bureaucracy. It has an enormous degree of flexibility and is still free-formed in many ways. Quite frankly, I need a dose of that. ■

RECIPIENTS OF THE 1995 NIH FELLOWS AWARD FOR RESEARCH EXCELLENCE

DCRT
Amir H. Gandjbakhche, "In vivo optical tomography."

NCI
Mehmet Sitki Copur, "Thymidylate synthase and p53 mRNA form a ribonucleoprotein complex."

Richard Gontarek, "A mutation in an equine infectious anemia virus exonic splicing enhancer results in rev-independent exon skipping."

Allan Hildensheim, "Evaluation of conventional and automated exfoliative cytology, cervicography, and HPV DNA testing as cervical cancer screening tools in a population-based study of 10,000 women in Costa Rica."

Leslie B. King, "A targeted glucocorticoid receptor antisense transgene enhances apoptotic thymocyte deletion."

Tosio Tsukiyama, "Purification of an ATP-dependent nucleosome rearrangement factor."

Nanping Weng,"Human naive and memory lymphocytes differ in telomeric length and replicative memory."

NCHGR
Bruce A. Bunnell, "Optimization of transduction efficiency of human CD4+ peripheral blood lymphocytes."

NEI
Qian Li, "Expression of phospholipase A25 (PLA25) in murine allergic conjuctivitis: kinetics and modulation."

NHLBI
Zaiad Abassi, "Pulmonary and renal neutral endopeptidase EC3.4.24.11 in rats with experimental heart failure."

Sandra Lewisch, "Detection of 2-oxo-histidine in biological samples."

Anna Zolkiewska, "Processing an ADP-ribosylated integrin alpha-7 in skeletal muscle myotubes."

NIA
Chavali Balagopalakrishna, "Mechanisms of the displacement of bound oxygen from hemoglobin as an O_2 radical."

Boyu Zhao, "Neuronal cell death induced by mutant amyloid precursor protein via apoptosis."

NIAAA
Robert Pawlosky, "Moderate alcohol consumption in rhesus monkeys increases the levels of plasma 8-isoprostane and 4-hydroxy-nonenal and alters fatty acyl composition of the plasma lipoproteins and erythrocytes."

Benjamin Roberts, "Induction of CYP2E1, a cytochrome p450 enzyme, by ethanol."

NIAID
David Dorwood, "Activation and killing of cultured human B-cells by virulent *Borrelia burgdorferi*."

Sharon H. Jackson, "Chronic granulomatous disease (CGD) in the mouse: the p47phox knockout."

Lin Yuan, "T-cell differentiation in fetal mice."

NICHD
Ruben Baler, "Physiological regulation of oncongene FRA-2: circadian to adrenergic to cyclic AMP control in the rat pineal gland."

Gianmaria Maccaferri, "Feedback LTD of inhibitory neurons controls the entorhinal input to the hippocampal CA1 region."

Michael Marks, "Identification of a lysosomal/endosomal targeting determinant in the cytoplasmic tail of H-2Mb, a key player in the MHC class II antigen processing pathway."

Forbes Porter, "Lhx2, a LIM homeodomain gene, is necessary for eye and erythroid development."

NIDDK
Richard Benya, "Receptor structural elements mediating gastrin-releasing peptide receptor regulation: internalization, down-regulation, and chronic desensitization."

Michael Yu Degtyarev, "Post-translational palmitoylation of G-protein α subunits."

NIEHS
Asad Umar, "A novel DNA repair activity corrects unpaired bases in mismatch repair +/- human-cell-free extracts."

NIMH
Jeffrey Disbrow Erickson, "Molecular cloning and mechanisms of vesicular neurotransmitter transporters."

Terrence Sills, "Individual differences in sucrose consumption predict individual differences in amphetamine-induced release of mesolimbic dopamine."

NINDS
Tanya Lehky, "Anti-Tac (1L2-α) antibody treatment for HTLV-1-associated myelopathy."

Michael Levin, "Detection of HTLV-1 sequences by PCR/in situ hybridization."

Norhiro Sadato, "Braille reading in the blind activates the visual cortex."

Michael Twery, "Dopamine D1 receptors and the regulation of basal ganglia output in rats with 6-hydroxydopamine-induced lesions of midbrain dopamine neurons." ■

BLAZING A TRAIL
continued from page 1.

tried to license it," says this inventor, who asked not to be named. "I do not know whether it is a problem of shortage of people, disorganization, or lack of motivation, but my personal experience has been that the service is nonexistent at OTT."

Other problems plaguing OTT, along with the biotech industry as a whole, range from conceptual issues surrounding the patentability of DNA sequences to delays at the U.S. Patent Office, which has seen an explosion in biotech patent applications in the past decade. For some basic scientists, the issues are less concrete, but no less heartfelt. They see NIH as the last refuge for pure basic research and note that with the increasing emphasis on commercial development of discoveries in molecular biology have come new problems dealing with access to genes, reagents, and other tools. They complain of an apparent chill on the free, uncensored exchange of ideas that occurred among scientists in an earlier era.

Freire is acutely aware of these concerns as well as a passle of other problems that must be addressed simultaneously — like improving her office's morale and hiring replacements for the 13 program staff members who have left OTT in the past 18 months for positions in industry, trade groups, law firms, and academic tech-transfer offices. "Staffing is a key" to solving OTT's problems, Freire contends, explaining that "at the moment we are just trying to get out from a terrible rate of attrition" that coincided with last year's HHS-wide hiring freeze. The intense scrutiny of an HHS Inspector General's review of OTT generated a list of 88 corrective administrative actions for the office, creating mountains of extra work and undermining OTT's morale.

"To their credit, these people [who are leaving OTT] are getting good jobs, and when they leave here, their caseload goes from handling 120 cases to 10 cases" at a time, Freire says. "NIH has a reputation as a wonderful training ground. If they can make it here, they'll make it anywhere." In addition to the large number of cases each tech-transfer officer handles, Freire notes, "we handle some of the most difficult cases in the industry." But she remains undaunted by such challenges, saying, "I find this incredibly exciting. I'm sure we will make mistakes — and learn from them — because we are trailblazing."

Freire, who holds a doctorate in biophysics from the University of Virginia in Charlottesville and who came to NIH from a position in charge of the tech-transfer office for the University of Maryland's Baltimore and Baltimore County campuses, says solving OTT's problems will not be painless. Her starting point has been examining NIH's tech-transfer process and whether the expectations of scientist-inventors and others are realistic. The next question, Freire says, is, "What are we doing wrong and right, internally, given the process?"

> **"I'M SURE WE WILL MAKE MISTAKES — AND LEARN FROM THEM — BECAUSE WE ARE TRAILBLAZING."**

"If it's things like phones and meeting Patent Office deadlines, we just have to fix them," Freire says. But other issues are only barely within OTT's influence. "In terms of the time it takes — three years, on average — to get a patent, that is process-driven by the times required by the Patent Office, the FDA, etc.," Freire says. "In the field of biotechnology, we are challenging everybody. The Patent Office ... is learning what questions to ask. ... That's another role of NIH — to push the envelope and suggest ways to handle these issues." Jack Spiegel, acting director of OTT's Division of Technology Development and Transfer, says the Public Health Service currently receives 250 to 300 reports of new inventions per year — mostly from NIH. Patent applications are submitted on about 150 inventions per year and typically cost $10,000 to $15,000 each to prepare, file, and steer through the application and approval process — if there are no significant challenges or questions raised.

Freire sees educating NIH researchers and working closely with the various institutes' scientific directors and technology-development coordinators as the keys to improving tech transfer. A major effort is underway to make "leaner and meaner" the institutes' portfolios of potentially patentable inventions. This means improving the balance between patenting and licensing. It will also mean asking scientific directors more and more often to relay the ego-shattering news that NIH won't be seeking a patent on every scientist's precious brainchild.

Freire says that NIH's would-be inventors must understand that only a tiny fraction of their clever concepts will become products. "Just consider the attrition rate from beginning to end for getting a product to market at a large pharmaceutical company — where product development is what they do for a living," Freire suggests. "If they churn out 60 projects a year, of that — if they're lucky — they will have one to two drugs in 10 years." As the scientific and biomedical research environment evolves, patent portfolios must also change, she says, "and the odds are small that something will make it all the way to market, even when it's not highly exploratory research" like much of the work coming out of NIH.

Freire's forthright approach appears to be winning over the scientific directors. After NICHD Scientific Director Arthur Levine and tech-transfer staffs from both NICHD and OTT spent a long day reviewing NICHD's extensive tech-transfer portfolio, Levine concluded that "Freire's background in fundamental science, the experience she gained at the University of Maryland, and her knowledge both of patent law and of the science marketplace combine to give her an exceptional sense of clarity, focus, and sensibility, which promise — for the first time — a truly effective and efficient OTT."

Freire also wants NIH scientists to understand that they are a key source of information on where to market rights to an invention. "At MIT, for example, 54% of the licenses come from researchers' contacts. And it's about 60% to 70% at the University of Maryland and Johns Hopkins," Freire says.

As OTT proceeds with these efforts, other critical tech-transfer issues are starting to sort themselves out favorably. In late February, after two years of active negotiation between OTT and major universities, NIH became the first signatory on a Universal Biological Materials Transfer Agreement (UBMTA), which is now being sent out for the universities to sign. UBMTA is expected to simplify and speed the sharing of research materials between scientists at signatory institutions. Also in February, access to gene sequences opened up dramatically when Merck & Co., in Whitehouse Station, N.J., and Washington University in St. Louis announced the release of 15,000 human expressed-sequence tags (ESTs) to the

public domain. The ESTs should be a boon for researchers seeking to map, identify, or find homologies for sequences they have found. The company's "Merck Gene Index" project will place 300,000 gene sequences in GenBank's EST division over the next 18 months.

On the basis of an extensive study by OTT's Deputy Director Barbara McGarey, NIH Director Harold Varmus persuaded HHS to strike the so-called reasonable-pricing clause from CRADAs and Exclusive License Agreements. McGarey found that the clause has blocked companies from entering into CRADAs because the firms fear that the government will dictate prices that prevent earning a profit on products emerging from the collaborations. She was unable to turn up a single instance in which the clause had served its purpose of keeping down prices on products flowing from NIH scientists' ideas.

Although some scientists may continue to debate the appropriate role for tech transfer at NIH, Freire says that for OTT there is no "either-or" question of supporting basic or applied research — both must be maintained — and the bottom line is clear: getting NIH's scientific discoveries turned into products that improve public health. "It's important that we don't lose the ivory tower," Freire says. "If we lose our basic research and our trailblazing, we lose the future." But she also points out that if there are no rewards for commercial developers or if the tech-transfer process is too frustrating and cumbersome, "You can lose products and, ultimately, better therapies for patients."

Deputy Director for Intramural Research Michael Gottesman's office assumed operational responsibility for OTT after Freire took the reins, allowing Sandy Chamblee, NIH's acting deputy director for science policy and technology transfer, to tackle some of the broader tech-transfer issues. Gottesman believes intramural science as a whole will profit from the changes at OTT, saying that Freire "knows the industry and the science. Her judgment and instincts are sound."

Reflecting on her first months at NIH, Freire says, "I feel like a kid in a candy store. This is awesome technology we are seeing. I'm really impressed with our portfolio — and I've seen some of the best. This is so rich, we have a moral obligation to find a partner to bring the technology out." ■

THE PATENT CHECK LIST

The key to winning a patent is being able to prove that you were the first person on earth to come up with the idea for a novel, useful product that is neither an obvious recombination of other inventions nor something everyone else knows about. Here are a few do's and don'ts from Jack Spiegel, acting director of OTT's Division of Technology Development and Transfer:

Do's

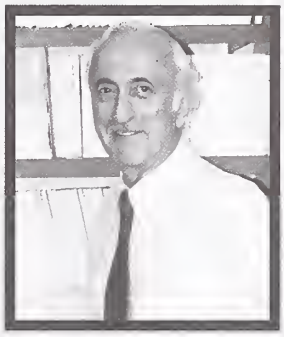
- **Do keep good lab records.** Save all notes, e-mail messages, and letters outlining the conception of an invention with potential commercial importance or wide-ranging benefits for public health. Each day, make sure to date and sign lab notebooks outlining experiments involving potentially patentable inventions. It's also a good idea to have an outside "witness" sign your experimental log daily — perhaps someone else in the lab.
- **Do let OTT know about your inventions**. Each institute, center, or division has a technology-development coordinator whom you should contact as soon as you begin to draft an abstract or paper discussing your work.
- **Do take patent application deadlines seriously.** Delays in submitting the appropriate documentation can cost NIH thousands of dollars and may even cost you the patent.
- **Do determine who your co-inventors are.** Remember that co-authorship is not synonymous with co-invention. To be considered an inventor, you must have made an important and unique intellectual contribution to the development of a potentially patentable product. Also, unless specified otherwise, NIH patent agreements divide royalties equally among all inventors. So, for example, if one of four inventors deserves 75 percent of the credit — and, thereby, 75 percent of the money — for the invention, it must be spelled out in the agreement. If not, he or she, along with the other inventors, will each get 25 percent.
- **Do remain actively involved in the licensing process.** Getting a patent is only half the battle in technology transfer. The real test of whether your invention will fly in the commercial world is if — and how — it gets licensed to a private firm. An invention is most likely to be a commercial success if inventors continue to share their insights and expertise — including the names of firms that may be interested in the invention — with OTT during the licensing process.

Don'ts

- **Don't talk about your invention before patent filing.** OTT strongly recommends not discussing your invention with people outside NIH unless you have them sign confidentiality forms, available from your technology-development coordinator.
- **Don't forget that meeting abstracts count as publications**. Any written disclosure of your invention — whether it is printed in a meeting abstract book or in a scientific journal — can be used by other parties to initiate foreign patent rights. Give OTT several months' notice in advance of publication so NIH can get a head start in the highly competitive, international patent process.
- **Don't be afraid of looking stupid**. OTT urges you to notify your technology-development coordinator even if you think there's only a slim chance your invention is patentable. According to OTT, scientists are often not the best judges of what is patentable. In addition, OTT may be able to exploit routes other than the patent process for transferring your invention into use in the private sector.
- **Don't trust non-NIH collaborators to look out for you.** Even if you have a fantastic scientific relationship with collaborators outside NIH, OTT warns you not to assume that their universities or companies will act in your best interest when it comes to the patent process. Promptly notify OTT of any collaborations in which you have made substantial intellectual contributions or innovative technical contributions to a potentially patentable invention.
- **Don't expect to get fabulously rich.** Currently, the most an NIH scientist can collect in royalties from a patented invention that he or she helped to develop is $100,000 a year. Even if you leave the government, you cannot collect more. ■

British Honor NICHD Researcher

The British Society for Endocrinology recently awarded its prestigious Dale Medal to Kevin J. Catt, head of NICHD's Endocrinology and Reproduction Research Branch, for his contributions to endocrinology over the past 30 years. Catt, an international authority on the physiology and molecular biology of the hypothalamo-pituitary-adrenal and -gonadal systems, has been one of the 1,000 most-cited contemporary scientists for nearly half his career. His current research centers on signal transduction in pituitary gonadotrophs, mechanisms of gonadotropin-releasing hormone secretion from hypothalamic neurons, and the mechanism of action of angiotensin II. ■



Lorna Heartley

Kevin J. Catt

A SLPI DEFENSE AGAINST HIV
continued from page 9.

activity. If these earlier data are correct, LMI (SLPI) concentrations in these various tissues may be roughly inversely related to the susceptibility to transmission for these tissues, and it is conceivable that SLPI evolved as a key protective ingredient in saliva, bronchial mucous, and cervical secretions, which coat the surfaces of the most common routes of access to the body by viruses, retroviruses, and other microorganisms. Exogenous augmentation of SLPI concentrations — either by parenteral or topical application or through somatic gene therapy to boost expression at mucosal sites possessing subantiviral activity — may heighten SLPI's effectiveness as a defensive shield.

At the very least, probing the SLPI barricade against HIV will help us dissect pathways of viral adherence and internalization. At best, understanding SLPI may lead to the development of new drugs that combat HIV and possibly other invasive microorganisms in a novel way. ■

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What's Cool? Internet Information Expo

Whether you're a greenhorn or an old hand when it comes to computer networking, you'll probably want to check out NIH's first Internet Information Expo. The event, hosted by DCRT, will run from 8:30 a.m. to 4:00 p.m. on May 9 at the Conference Center in the Natcher Building. No registration is needed to take part in the wide range of 1/2- to 1- hour seminars dealing with various aspects of the World Wide Web, Gopher, and computer networking at NIH. There will also be hands-on and demonstration areas that will allow attendees to try out and see exciting Internet applications. For more information, contact DCRT (phone: 594-DCRT; e-mail: 4dcrt@nih.gov; World Wide Web: http://www.nih.gov/dcrt/expo/). ■

THE WORLD WIDE WEB
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While all this reliance on computer technology may seem the stuff of an Orwellian nightmare, the Internet does not have to be a mechanism for making science impersonal. It can bring scientists together. Anyone can now buy a small, relatively cheap video camera to attach to your own computer and take part in the on-line video conferencing already occurring over the Internet. With the addition of on-line language interpreters, video conferencing should open a new arena for collaboration and interaction in the international scientific community.

Because we believe that the World Wide Web is rapidly becoming an integral part of scientific endeavor, we would like to challenge all intramural scientists to assist us in creating the first NIH Scientific Poster Conference Page on the World Wide Web. The purpose of this page will be to provide references to a wide array of Web pages that feature posters describing ground-breaking research performed at NIH — in essence, a virtual and continuous poster session. To make this idea a reality, we need your suggestions about how the NIH Scientific Poster Conference Page should be set up and what sorts of research it should feature, and, most importantly, we need you to tell us about research findings that you have already posted or are planning to put on the Web. Together, we as NIH researchers can use the Web to showcase — and advance — our scientific achievements. ■

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Contracting Out the Clinical Center?

The rumors that have been swirling around the Clinical Center for months are now official. As part of its ongoing drive to "reinvent" government, the Clinton Administration has indeed asked NIH to consider the possibility of contracting out the service components of the Clinical Center. And the truth may prove not quite as frightening as many had imagined.

According to a March 29 memo from Clinical Center Director John Gallin, a contract arrangement would be considered only if it is financially sound and could be done without compromising the quality of clinical care and research. The process of evaluating whether Clinical Center services should be turned over to a private contractor is expected to take about two years, although some intermediary decisions may be made between now and then.

Another encouraging note for clinical researchers is that the HHS official who is leading the effort to examine the Clinical Center's operations is Health Care Financing Administration Deputy Administrator Helen Smits — a physician who has extensive hospital management experience and who has served on the faculties of Yale University School of Medicine in New Haven, Conn., and the University of Connecticut Health Center in Farmington. Smits, a former member of the Board of Commissioners of the Joint Commission on Accreditation of Health Care Organizations, visited the Clinical Center March 30 and is expected to return several times to familiarize herself with its focus and concerns.

Gallin describes Smits' initial visit as "very positive." According to Gallin, Smits described herself as leading an "options team" to identify administrative obstacles that the Clinical Center faces in carrying out its mission and to develop the best process for evaluating the options to correct the problems. ■

FAX-BACK

In this issue, we are asking for your feedback in four areas: the future of NIH's physical environment, technology transfer, tips and suggestions for our Hot Methods Clinic, and intramural research outside Bethesda. **Fax your responses or comments on other intramural research concerns to 402-4303** or mail them to us at Building 1, Room 334.

In Future Issues. . .

- Intersecting Orbits: NIH Meets NASA
- The Revamped RAC: What Does It Mean For Intramural Gene Therapy?
- Simplifying The Scientific Procurement Process
- Beyond Bethesda: The Life & Times of The Other Intramurals

1) What are your reactions to the "Shape of Things to Come" commentary? What specific suggestions do you have for improving NIH's physical environment over the next 20 years?

2) From a scientist's perspective, what do you view as the most critical issues in technology transfer at NIH? What changes might make the tech-transfer process easier for and more attractive to scientists?

3) Do you have any suggestions or comments about the NIH Scientific Poster Conference Page on the World Wide Web proposed in this issue's Hot Methods Clinic? What updates can you provide on previous Hot Methods? What techniques would you like to see covered in future issues?

4) We are planning a series of articles on intramural research programs located outside Bethesda. What programs and issues would you like to see covered in such articles? What steps should be taken to improve the flow of scientific information between Bethesda and outlying campuses?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 334, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; e-mail: KOLBERGR or HOOPERC@od1em1.od.nih.gov

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